Combining Covariate Adjustment with Group Sequential Designs to Improve Randomized Trial Efficiency

UNIVERSITEIT GENT

Kelly Van Lancker
Joint work with
Michael Rosenblum and Josh Betz

JOHNS HOPKINS BLOOMBERG SCHOOL of PUBLIC HEALTH

Covariate Adjustment

- **Covariate adjustment** is a statistical analysis method with high potential to **improve precision** for many trials.
  - **Pre-planned** adjustment for baseline variables when estimating **average treatment effect**.
  - Estimand is same as when using unadjusted estimator (e.g., difference in means).
  - **Goal**: avoid making any model assumptions beyond what's assumed for unadjusted estimator (**robustness to model misspecification**).

(e.g., Koch et al., 1998; Yang and Tsiatis, 2001; Rubin and van der Laan, 2008; Tsiatis et al., 2008; Moore and van der Laan, 2009b,a; Zhang, 2015; Jiang et al., 2018; Benkeser et al., 2020)

Group Sequential Designs

- A commonly used type of clinical trial design that involves **pre-planned interim analyses**
  - where the trial can be **stopped early** for efficacy or futility.
- Prevalent in confirmatory clinical trials for **ethical and efficiency reasons** as they potentially **save time and resources** by allowing early termination of the trial.

Problem Setting

- **Combination** of covariate adjustment and group sequential designs has the **potential to offer the benefits of both methods**:
    - using covariate adjusted estimators at interim and final analyses of a group sequential design.
- Several **challenges** involved in combining these two approaches.

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   - This is the case when models used to construct the estimators are misspecified.
2. The **uncertainty** at the design stage about the **amount of precision gain and corresponding sample size reduction**.
   - Proposals have been made to use external trial data to estimate the precision gain.
   - Nevertheless, an incorrect projection of a covariate's prognostic value risks an over- or underpowered future trial.
   - This is also an obstacle in trials without interim analyses.

Endpoints, Estimands and Estimators

- The proposal works for **all types of common outcomes**
  - e.g., continuous, binary, ordinal, and time-to-event
- The proposal accommodates **any estimand**, including
  - risk difference, relative risk and odds ratio for binary outcomes,
  - difference in restricted mean survival times and relative risk for time-to-event outcomes,
  - ...
- The proposal will be applicable to **any (adjusted and unadjusted) estimator** as long as it is regular and asymptotically linear (RAL) and consistent for the estimand of interest.
  - e.g., *G-computation* estimator (as suggested in the recent FDA draft guidance on covariate adjustment)

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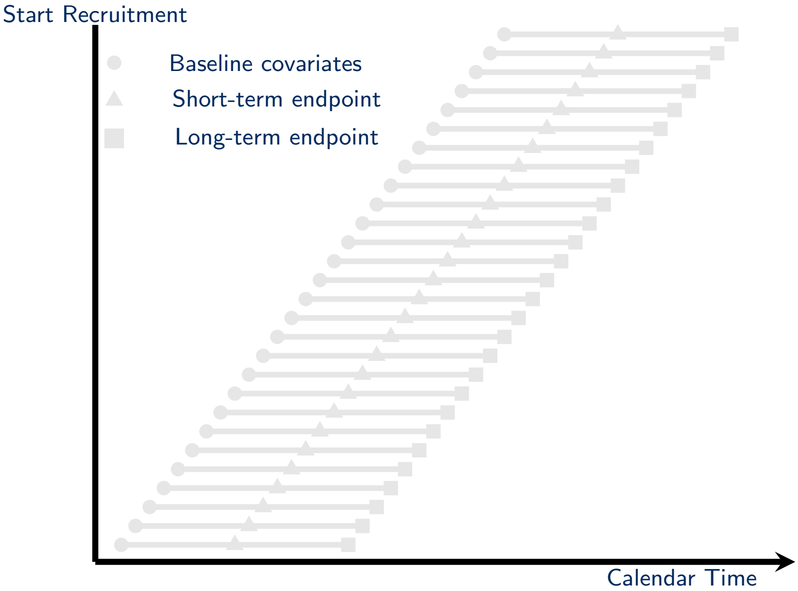
- Estimator: G-computation/Standardization
  1. Fit logistic regression model for
  $$P(Y=1|A,B) = logit^{-1}(\gamma_0 + \gamma_1 A + \gamma_2 B).$$
  2. Compute standardized estimators for treatment specific means
     - $\hat{E}\,(Y|A=1) = \frac{1}{n}\sum_{i=1}^{n} logit^{-1}(\hat{\gamma}_0 + \hat{\gamma}_1 + \hat{\gamma}_2 B_i)$
     - $\hat{E}\,(Y|A=0) = \frac{1}{n}\sum_{i=1}^{n} logit^{-1}(\hat{\gamma}_0 + \hat{\gamma}_2 B_i)$
  3. Calculate $\hat{\theta} = \hat{E}\,(Y|A=1) - \hat{E}\,(Y|A=0)$

Group Sequential Design



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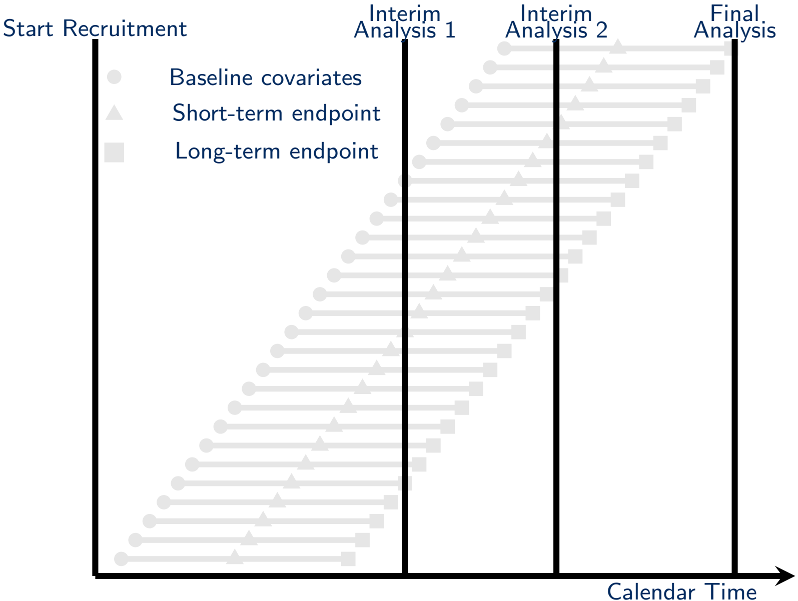

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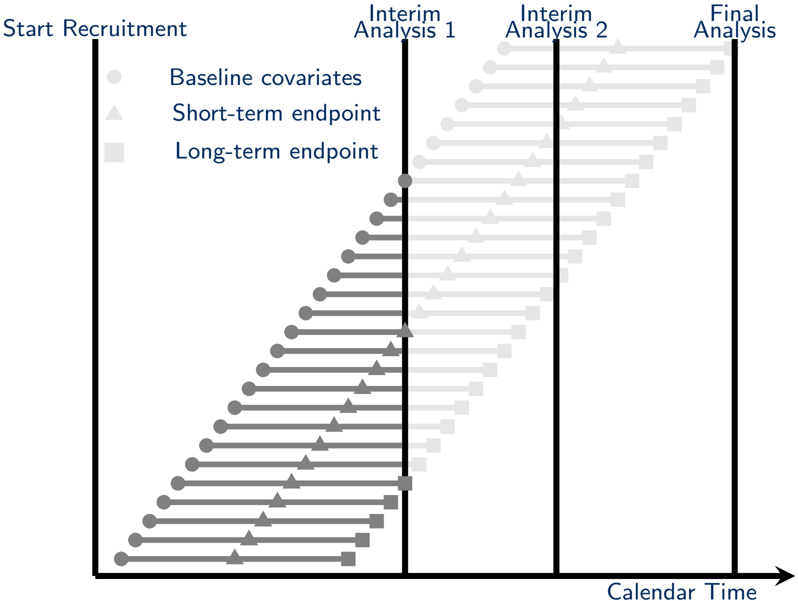

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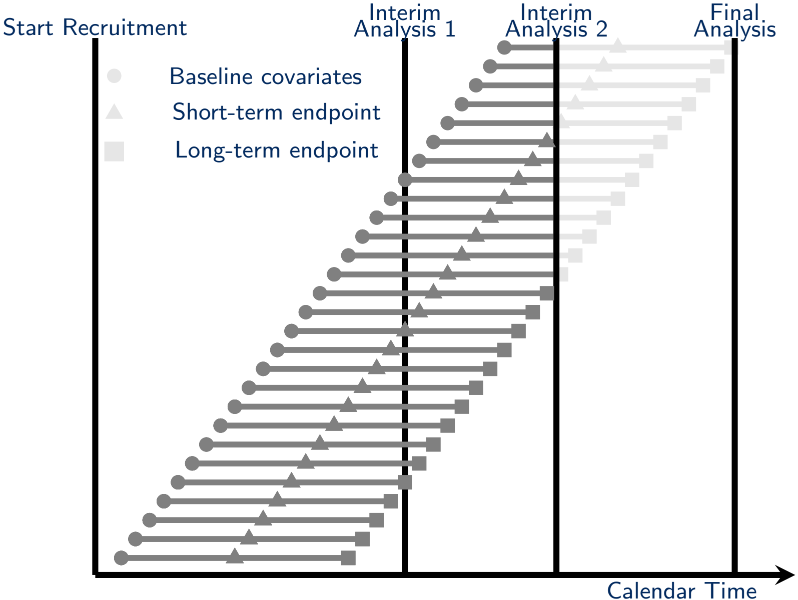

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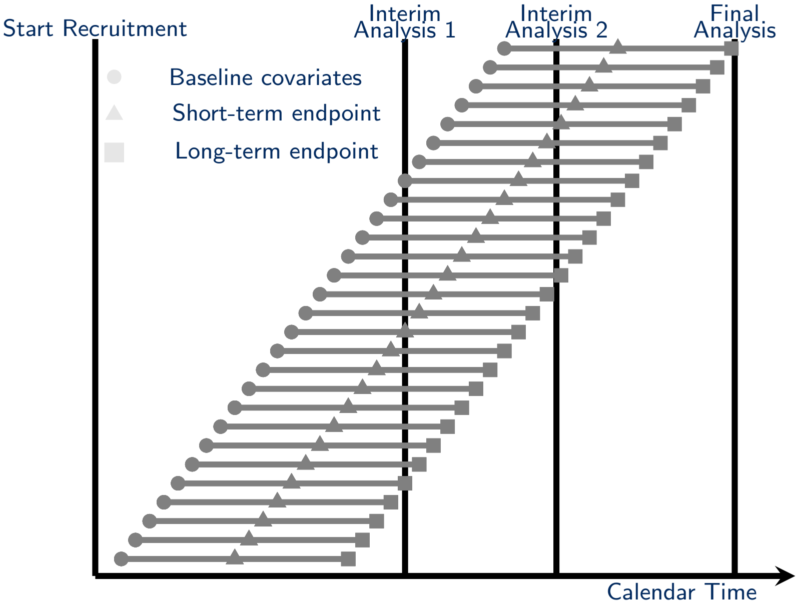

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Group Sequential Design

- A group sequential design can **reduce the length** of a Phase 3 trial
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  - Faster access to effective treatments
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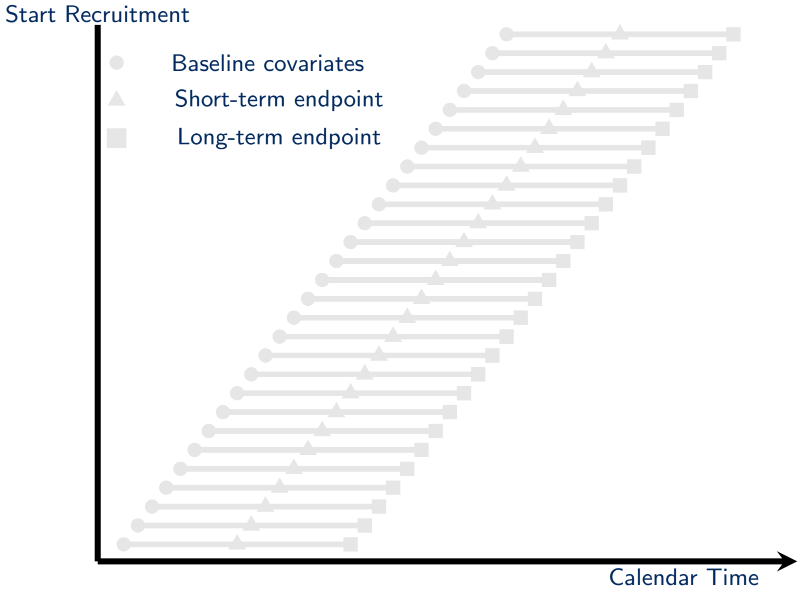
  - **Saving resources**
- Multiple looks at accumulating data **increase type I error**
  - Lower significant thresholds needs to be used for the interim analyses.
  - There are a range of methods for defining the critical values for interim analyses.

(Pocock, 1977; O'Brien and Fleming, 1979; Lan and DeMets, 1983)

Independent Increments



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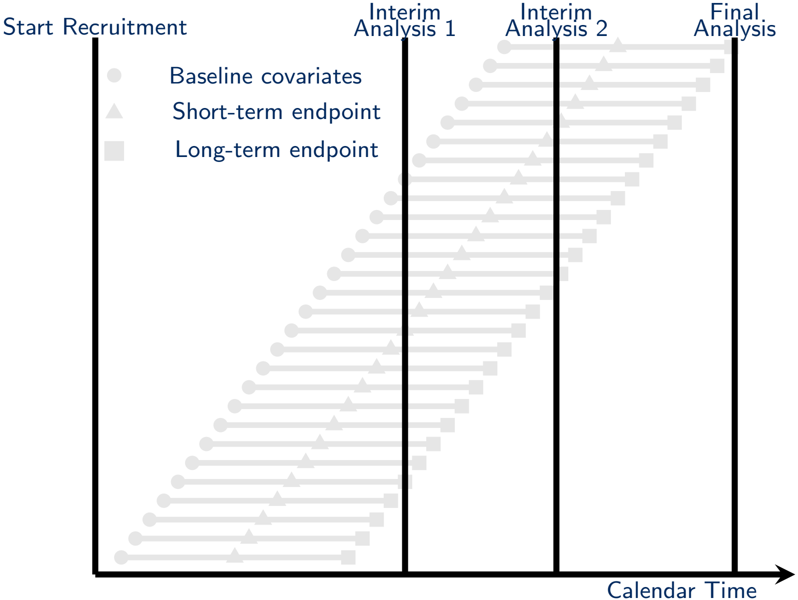

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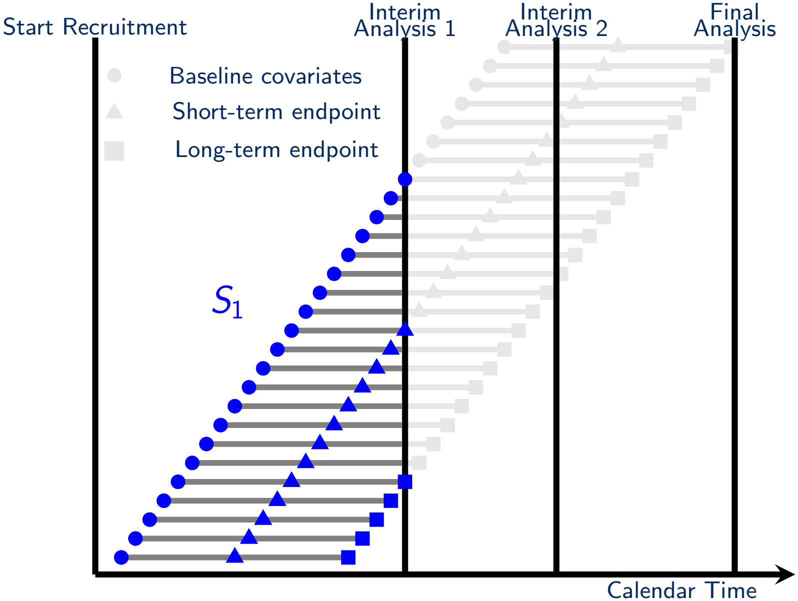

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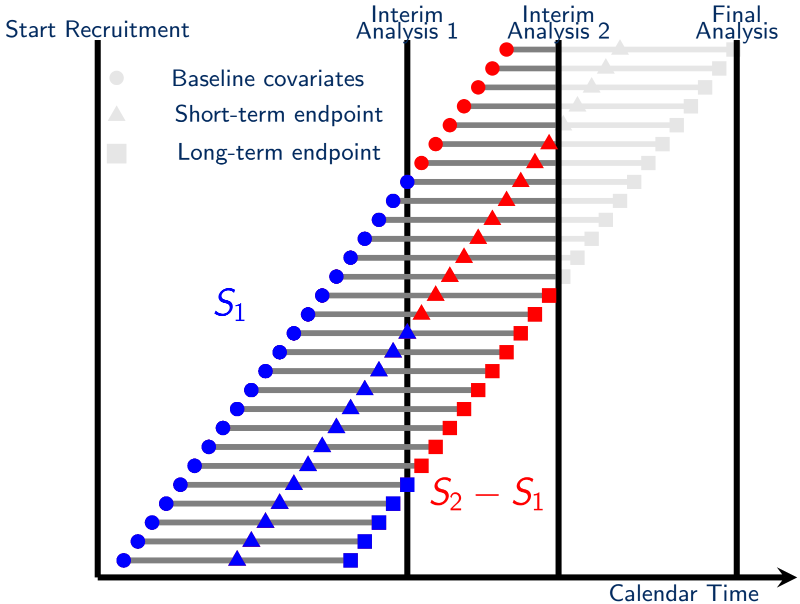

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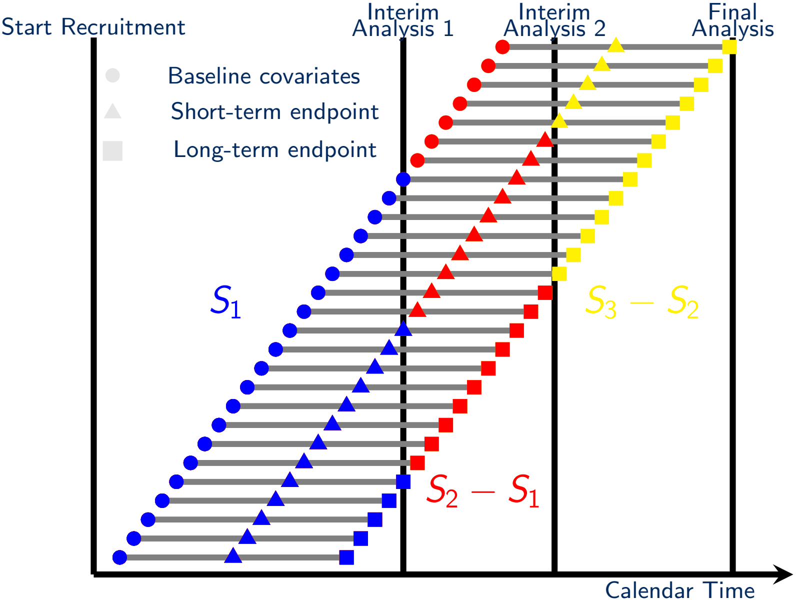

Group Sequential Designs: Incompatibility

- Unfortunately, a sequence of RAL estimators $(\hat{\theta}_{t_1}, \ldots, \hat{\theta}_{t_K})$ do not necessarily have the independent increments property.
- This was for example shown for:
  - Estimators based on generalized estimating equations (Shoben and Emerson, 2014)
  - G-computation and TMLE estimators when working models are misspecified (Rosenblum et al., 2015)
  - A long list of further counterexamples is provided by Jennison and Turnbull (1997) and Kim and Tsiatis (2020)

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  - A long list of further counterexamples is provided by Jennison and Turnbull (1997) and Kim and Tsiatis (2020)
- Proposal: **modifying** any RAL estimator so that it has the **independent increments property** and also has **equal or smaller variance than the original estimator**.

Proposal: Motivation

- **Goal:** Obtain at each analysis time t_k an estimator $\widetilde{\theta}_{t_k}$ that
  1. is consistent for θ,
  2. is asymptotically linear,
  3. is asymptotically normal,
  4. is asymptotically as or more precise as the original estimator $\widehat{\theta}_{t_k}$, and
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- We will focus on finding the **linear combination**

$$\widehat{\theta}_{t_k} - \sum_{k'=1}^{k-1} \lambda_{k'}^{(k)} (\widehat{\theta}_{t_k} - \widehat{\theta}_{t_{k'}})$$

with **minimal variance**.

Thank you for your attention!

Interested? https://doi.org/10.48550/arXiv.2201.12921
E-mail: kelly.vanlancker@ugent.be
Website: kellyvanlancker.com

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